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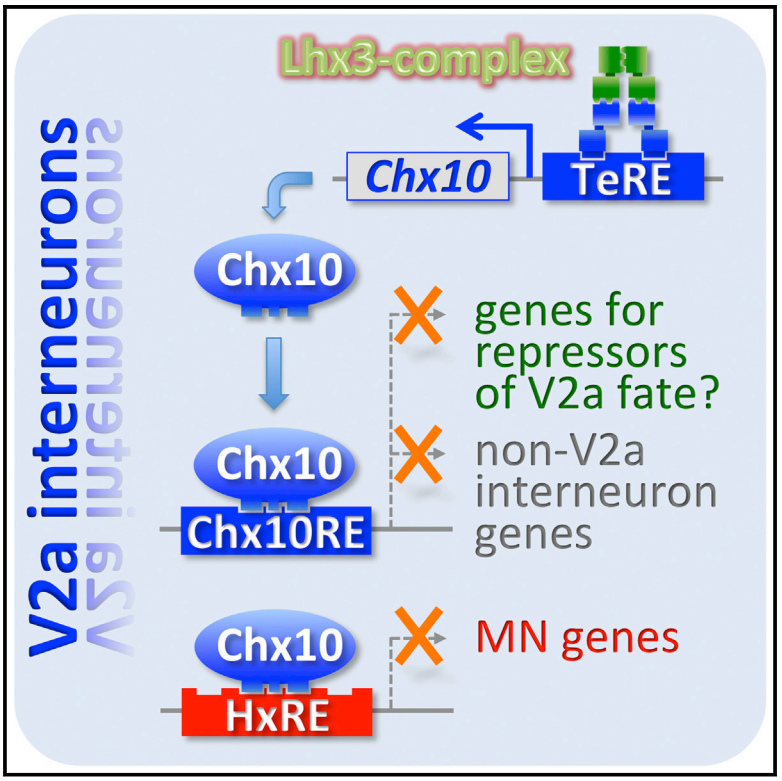
Chx10 Consolidates V2a Interneuron Identity through Two Distinct Gene Repression Modes

Graphical Abstract



Authors

Yoanne M. Clovis, So Yeon Seo, Ji-sun Kwon, ..., Jae W. Lee, Seunghee Lee, Soo-Kyung Lee

Correspondence

leeseung@snu.ac.kr (S.L.), leesoo@ohsu.edu (S.-K.L.)

In Brief

Clovis et al. describe the mechanism through which spinal V2a interneurons are specified. They find that the best-known marker for V2a interneurons, Chx10, is the major determinant of V2a fate specification. Chx10 upregulates the expression of V2a interneuron genes while suppressing the expression of non-V2a interneuron and motor neuron genes.

Highlights

- Chx10 is required for Lhx3 to specify V2a interneurons
- Chx10 upregulates the expression of V2a interneuron genes
- Chx10 suppresses the expression of non-V2a interneuron and motor neuron genes
- These activities enable Chx10 to effectively consolidate the V2a pathway

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Chx10 Consolidates V2a Interneuron Identity through Two Distinct Gene Repression Modes

Yoanne M. Clovis,[1] So Yeon Seo,[3] Ji-sun Kwon,[1] Jennifer C. Rhee,[3] Sujeong Yeo,[3] Jae W. Lee,[1] Seunghee Lee,[3,*] and Soo-Kyung Lee[1,2,*]

[1]Pediatric Neuroscience Research Program, Papé Family Pediatric Research Institute, Department of Pediatrics
[2]Vollum Institute
Oregon Health and Science University, Portland, OR 97239, USA
[3]College of Pharmacy and Research Institute of Pharmaceutical Sciences, Seoul National University, Seoul 151-742, Korea
*Correspondence: leeseung@snu.ac.kr (S.L.), leesoo@ohsu.edu (S.-K.L.)
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SUMMARY

During development, two cell types born from closely related progenitor pools often express identical transcriptional regulators despite their completely distinct characteristics. This phenomenon implies the need for a mechanism that operates to segregate the identities of the two cell types throughout differentiation after initial fate commitment. To understand this mechanism, we investigated the fate specification of spinal V2a interneurons, which share important developmental genes with motor neurons (MNs). We demonstrate that the paired homeodomain factor Chx10 functions as a critical determinant for V2a fate and is required to consolidate V2a identity in postmitotic neurons. Chx10 actively promotes V2a fate, downstream of the LIM-homeodomain factor Lhx3, while concomitantly suppressing the MN developmental program by preventing the MN-specific transcription complex from binding and activating MN genes. This dual activity enables Chx10 to effectively separate the V2a and MN pathways. Our study uncovers a widely applicable gene regulatory principle for segregating related cell fates.

INTRODUCTION

During embryonic organogenesis, many cell types are born in a spatially and temporally controlled manner to form a functional tissue. One of the most fundamental questions in developmental biology is how closely related cell types are produced from similar progenitors and yet acquire and maintain completely distinct cell identities during later stages of organogenesis. This relatively poorly understood process involves intricate gene regulatory networks that operate during sequential steps of cell fate commitment, specification, and differentiation.

The gene regulatory networks for motor neurons (MNs) and V2a interneurons (V2aINs) provide an ideal platform to address this topic. The morphogen Sonic hedgehog (shh) is secreted from the notochord and floor plate and patterns neuroepithelial cells along the dorso-ventral axis, leading to the formation of the two neighboring progenitor domains, the pMN and p2 domains (Figure 1A) (Catela et al., 2015; Lee and Pfaff, 2001). Progenitor cells in the pMN and p2 domains produce MNs and V2aINs, respectively. While pMN cells upregulate the LIM-homeodomain (HD) transcription factors Isl1 and Lhx3 right before differentiation to MNs, p2 cells upregulate Lhx3, but not Isl1, shortly before cell-cycle exit (Figure 1A) (Ericson et al., 1992; Pfaff et al., 1996; Sharma et al., 1998; Tsuchida et al., 1994). Isl1 and Lhx3 form a hexameric complex with a self-dimerizing cofactor NLI, herein referred to as the Isl1-Lhx3-complex (also known as the MN-hexamer; Figure 1A) (Lee et al., 2008; Lee and Pfaff, 2003; Seo et al., 2015; Thaler et al., 2002). The Isl1-Lhx3-complex directly controls a wide range of MN genes and plays crucial roles in the fate specification of MNs (Cho et al., 2014; Lee et al., 2004, 2008, 2012, 2013; Lee and Pfaff, 2003; Mazzoni et al., 2013; Thaler et al., 2002; Thiebes et al., 2015). The misexpression of Lhx3 alone drives formation of ectopic V2aINs marked by Chx10 in the developing spinal cord (Tanabe et al., 1998; Thaler et al., 2002). Lhx3 also binds to NLI and forms a tetrameric complex herein referred to as Lhx3-complex (also known as the V2-tetramer; Figure 1A) (Joshi et al., 2009; Thaler et al., 2002). It has remained unclear whether the Lhx3-complex directly induces the expression of an array of V2aIN genes, similarly to the Isl1-Lhx3-complex, or whether it indirectly triggers V2aIN fate by upregulating other transcription factors that serve as its downstream effectors to induce V2a identity. The segregation of pMN and p2 domains is initiated by the cross-repressive actions of two transcription factors, Olig2 and Irx3, in the progenitor cells (Lee and Pfaff, 2001; Lu et al., 2002; Novitch et al., 2001; Zhou and Anderson, 2002). Interestingly, pMN cells and newborn MNs maintain cell fate plasticity and can switch their fate into V2aINs when the MN pathway is dysregulated (Arber et al., 1999; Lee et al., 2008; Lu et al., 2002; Song et al., 2009; Thaler et al., 1999; Zhou and Anderson, 2002). These results strongly suggest that the mechanisms that separate MN and V2aIN identities continue to operate even after the progenitor cells are committed to MN or V2aIN fate. However, the precise regulatory mechanisms that consolidate V2aIN fate after cell-cycle exit have yet to be clarified.

While Lhx3 triggers the V2aIN fate specification, it is also expressed in MNs (Sharma et al., 1998; Tsuchida et al., 1994), thus warranting additional mechanisms to block erroneous activation of MN genes in differentiating V2aINs. It is possible that